For Claim Rej ctions - 35 USC § 102

(1) Claims 13, 15, 16, 24, 27, 29, 33, 34, 36, 39, and 41 stand rejected under 35 U.S.C. 102(b) as the claims are said being anticipated by Helmus et al (US 5,447,724).

Helmus was cited, in the Final Office Action of 09/05/2003 (hereafter "rejection"), for teaching all the claimed subject matter including an implantable medical device (col. 3, lines 31), having a tissue-contacting surface formed of polyurethane or silicone (col. 2, lines 41-42) which has a drug such as heparin (col. 6, line 51) or a steroid (col. 6, line 56) intimately mixed into it (col. 4, lines 20-24 and col. 9, lines 45-46), wherein the drug makes up 2% by weight of the material (col. 7, lines 57-62).

The rejection also noted that Helmus' col. 7, lines 57-62 as indeed to specify the OUTER layer, not the reservoir layer. The rejection stated that in col. 7, lines 57-62, Helmus teaches that the agent in the outer layer is put there to produce a "gradual release effect" alluding to the slower release of the agent at first from the outer layer and gradual increase in the release rate as the more concentrated stores of the same agent start to seep through the outer layer from the inner reservoir layer. The rejection further contended that since this teaches that the agent in the outer layer can be the same as in the inner layer, Helmus' teaching of the reservoir agent being a steroid (col. 6, line 55) is interpreted as referring to physiologically active agents in BOTH the reservoir and outer layer.

Applicants' respectfully traverse. " Helmus does not expressly teach that the tissue-contacting polymer surface of the catheter is intimately mixed with the drug such that a non-porous release system is formed with the agent [see claim amendments adding a 'non-porous release system is formed with the agent"].

The examiner 's cites col.4, lines 20-24 and col. 9., lines 45-46 as teaching the drug is intimately mixed with the polymer:

> The tissue exposed portion is formed by thermal methods such as thermal extrusion or molding a mixture of the active agent and the reservoir polymer and/or extrusion or molding of a misture of the elutable component and the surface layer polymer [col., lines 20-24]

> Additionally, articles may be formed by thermal means such as injection molding a mixture of polymer and active agent. [col.9, lines 45-46]

Applicants respectfully disagree that the cited references teach what the examiner indicates. Because the Examiner finds that the polymer and active agent are mixed, it is concluded that they intimately mixed as meant by the applicants. Applicants claims are directed to a polymer system where the agent and the polymer when mixed do not form a porous polymer release system. Helmus teaches a porous drug release system. Helmus uses poragens to form pores in the polymer that serve as reservoirs for the drug. Helmus also uses these pores as the major mechanism for drug release. The pores can be created either by an added agent or the drug itself. However, the fact that the agent and the polymer are mixed does not determine whether the composition forms a porous network or a non-porous release system. This is determined by the appropriate selection of drug and polymer. Helmus list a group of drugs that may be used to form porous networks, however, he only exemplifies Heparin in polyurethane catheters to form a porous type reservoir release systems.

Applicants refer Examiner to the limitation that a "intimately mixed agent" would teach away from Helmus. Helmus teaches a pore structure of surface-contacting layer (i.e., outer layer) defines metering outward passages constructed to control the outward migration of the agent from the reservoir (i.e., inner layer) (col. 1, lines 39-46; col 1, lines 51-54; col. 3, lines 20-22; col. 5, lines 40-42; col. 5. lines 49-51; col. 5, lines 66-68; col. 7, lines 4-6; and Figs. 1a, 1b, 1c, 2a, 2b, and 2c). "Intimate mixing" would result homogenous disperse of the agent and ultimately destroy Helmus' passage concept. In other words, the limitation "intimate mixing" is not only unnecessary but also likely undesirable in Helmus. It would be also contrary to one of the ordinary skill in the art to practice "intimate mixing of the agent" when the result could destroy the intended structure and purpose. Applicants have added further effect to this meaning of the claims by further specifying that steroidal anti-inflammatory agent is intimately mixed with said polymer <u>such that a non-porous polymer release system is formed with said agent</u> .

In summary, the claim "tissue-contacting surface of the catheter comprises

a polymer in which a steroidal agent is intimately mixed with said polymer such that a non-porous polymer release system is formed with said agent" is not expressly nor inherently disclosed in Helmus. Therefore, the previous version of claims 13, 15, 16, 24, 27, 29, 33, 34, 36, 39, and 41 cannot be anticipated by Helmus et al. (US 5,447,724). Nevertheless, Applicants are willing to amend claims 13, 27, 29, and 33 as stated above. Such amendment would further distinguish the present invention from inferential elements contended in the rejection. As amended, claims 13, 27, 29, 33, and their dependant claims 15, 16, 24, 34, 36, 39, 41 would have overcome the rejection. Applications thus submit that the rejection of claims 13, 15, 16, 24, 27, 29, 33, 34, 36, 39, and 41 under 35 U.S.C. §102(b) should be withdrawn.

Claim Rejections - 35 USC § 103

(1) Claims 37, and 43 stand rejected under 35 U.S.C. 103(a) as the claims are said being unpatentable over Helmus et al (US 5,447,724).

The rejection noted that Helmus teaches all the claimed subject matter except for the slightly lower concentrations in claims 37 and 43. Helmus was also cited for teaching 2% of the material is the drug, whereas the (present) claims call for a maximum of 1 %. The rejection further stated that in a tissue-contacting wall of a catheter, the amounts of a drug that are needed to achieve a desired release rate vary somewhat based on the specific material that the drug is being mixed into, and also how the catheter was formed (i.e. extrusion process, etc.). The examiner then took the position that it would have been obvious to one of ordinary skill in the art to vary the weight percentage of a drug such a small amount in order to achieve a desired release rate depending the polymer being used and the manufacturing on process (temperature, curing, etc) used to make the catheter.

Applicants respectfully traverse. Helmus teaches that the elutable component in the outer layer may be physiologically active agent (col. 7, lines 57-59). More particularly, it is preferred to incorporate a minor amount, for example, about 2% by weight (col. 7, lines 60-62). The 0.1% - 1% agent in the present claims equates to 50% to 95% below Helmus' teaching. It does not appear to be obvious to one of ordinary skill in the art to further reduce the agent by 50% to

95% when the 2% has already been stated as "a minor amount."

Furthermore, as discussed above and also noted in the rejection, the agent in Helmus' outer layer is there to form pores and passages. It would not be obvious to one of ordinary skill in the art nor there is incentive to modify the 2% content when modification would destroy the structure and purpose of pores and passages.

Even more, the amended claims 13 and 29 would render claims 37 and 43 further unobvious over Helmus et al. (US 5,447,724), which does not teach the formation of "a non-porous polymer release system" with the agent for modulating degradation or tissue encapsulation of an indwelling catheter. Applications thus submit that the rejection of claims 37 and 43 under 35 U.S.C. §103(a) should be withdrawn.

(2) Claim 14 stands rejected under 35 U.S.C. 103(a) as the claim is said being unpatentable over Chait (US 5,727,555) in view of Helmus et al (US 5,447,724).

Chait was cited for teaching a catheter having an external fitting coupled to the proximal end, and helical coils as claimed. However, Chait lacks a layer with anti-inflammatory agent in it. Helmus was also found to teach an elongate body-inserted member with an anti-inflammatory agent imbedded in the tissue-contacting surface as discussed supra. The rejection then contended that it would have been obvious to one having ordinary skill in the art to form the catheter of Chait with the layered structure of Helmus in order to reduce inflammation in the treatment area, since formation of catheters with layers and with drug-saturated layers is well known in the art of catheters.

Applicants respectfully traverse. The mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *See* MPEP 2143.01, citing *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

Chait teaches a catheter having an external fitting coupled to the proximal end and helical coils, said helical coils to be reformed against an interior surface

of the body cavity (col. 2, lines 10-24), and intends to solve the problem of accidental dislodge during application (abstract). Chait, however, does not teach or suggest use of the active agent intimately mixed with polymer in its catheter having helical coils. In comparison, Helmus teaches using physiologically active agents to prevent adverse reactions to the device, but does not teach or suggest use helical coils to prevent dislodge of the device. Therefore, there is no suggestion or incentive for modifying Chait, Helmus, or combination of two to form applicants' claim 14. Likelihood of combing Chait and Helmus would be speculative or random occurrence. "Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Crown Operations Int'l, Ltd.* 289 F.3d at 1376 (Fed. Cir. 2002).

Furthermore, the amended claim 13 would render claim 14 further unobvious over Chait (US 5,727,555) in view of Helmus et al. (US 5,447,724), as neither reference teaches a non-porous polymer release system formed with the steroidal agent. Applications thus submit that the rejection of claims 14 under 35 U.S.C. §103(a) should be withdrawn.

(3) Claims 17-19, 38, and 44 stand rejected under 35 U.S.C. 103(a) as the claims are said being unpatentable over Helmus et al (US 5,447,724) in view of Fearnot et al. (US 5,609,629).

Helmus was cited for teaching all the claimed subject matter except for the steroid being a glucocortiocosteroid such as dexamethasone. Fearnot was cited for teaching the use of dexamethasone in a drug embedded outer layer of a catheter. The rejection then contended that it would have been obvious to one of ordinary skill in the art to use dexamethasone as taught by Fearnot as one of the steroids broadly mentioned by Helmus (col. 6, line 56) since dexamethasone is a well known anti-inflammatory steroid, and as demonstrated by Helmus it is know to use it as the bioactive component of a bioactive surface on a catheter.

The rejection also cited the definitions for "cortisone" and "glucocorticoid" from Stedman's medical Dictionary to demonstrate that Helmus teaches an "anti-inflammatory" steroid.

Applicants again respectfully traverse. The mere fact that references can

be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *See* MPEP 2143.01, citing *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). The proposed modification cannot change the principle of operation of a reference. MPEP 2143.01 citing *In re Ratti*, 270 F.2d 810 (CCPA 1959).

As mentioned above, the principle of operation of Helmus' outer layer, even if a physiologically active agent (e.g., glucocorticosteroid) shall be used, consists of pores for passages. Likewise, the principle of operation of Fearnot is to use a porous coating layer over the bioactive layer. Not only neither Fearnot nor Helmus suggests use anti-inflammatory agent on the tissue-contacting surface in form of intimate mixture with polymers, but also such modifications would change the principles of operation of Helmus and Fearnot.

Additionally, the amended claims 13 and 29 would render claims 17-19, 38, and 44 further unobvious over Helmus et al. (US 5,447,724) in view of Fearnot et al. (US 5,609,629), as neither reference teaches modulating degradation or tissue encapsulation of an indwelling catheter. Applications thus submit that the rejection of claims 17-19, 38, and 44 under 35 U.S.C. §103(a) should be withdrawn.

Summary

Applicants believe their present response address the outstanding issues presented by the examiner and respectfully request the finality of office action be withdrawn and all pending claims be allowed to issue.

Respectfully submitted,

3/4/04

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AMENDED CLAIMS
Version with Markings To Show Chang s Made
(37 CRF 1.121(c)(1)(ii))

Claims 1-12 cancelled.

Claim 13. (5X amended) An indwelling catheter comprising:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises a polymer in which a steroidal anti-inflammatory agent is intimately mixed in a concentration with said polymer such that a non-porous polymer release system is formed with said agent [in a concentration means] <u>for modulating degradation or tissue encapsulation of said catheter</u>.

Claim 14. The indwelling catheter of claim 13 further comprising one or more helical coils formed in the elongate body between the proximal and distal ends.

Claim 15. The indwelling catheter of claim 13 wherein the polymer is selected from the group of polyurethanes, silicones, polyamides, polyimides, polycarbonates, polyethers, polyesters, polyvinyl aromatics, polytetrafluoroethylenes, polyolefins, acrylic polymers or copolymers, vinyl halid polymers or copolymers, polyvinyl ethers, polyvinyl esters, polyvinyl ketones, polyvinylidine halides, polyacrylonitriles, copolymers of vinyl monomers with each other and olefins, and combinations thereof.

Claim 16. The indwelling catheter of claim 15 wherein the polymer is selected from the group of polyurethanes, silicones, or combination thereof.

Claim 17. The indwelling catheter of claim 13 wherein the anti-inflammatory agent is a glucocorticosteroid.

Claim 18. The indwelling catheter of claim 17 wherein the glucocorticosteroid is selected from the group of cortisol, cortisone, fludrocortisone, Prednisone, Prednisolone, 6α–methylprednisolone, triamcinolone, betamethasone, dexamethasone, beclomethasone, aclomethasone, amcinonide, clebethasol,

clocortolone, derivatives thereof, and salts thereof.

Claim 19. The indwelling catheter of claim 18 wherein the glucocorticosteroid is dexamethasone, a derivative thereof, or a salt thereof.

Claims 20-23 cancelled.

Claim 24. The indwelling catheter of claim 13 wherein the tissue-contacting surface further includes heparin.

Claims 25-26 cancelled.

Claim 27. (5X amended) A method of modulating tissue encapsulation of an indwelling catheter comprising implanting the indwelling catheter into a patient, wherein the indwelling catheter comprises:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises an overcoating of a polymer in which an effective amount of steroidal anti-inflammatory agent is intimately mixed such that a non-porous polymer release system is formed with said agent [means] in the polymer means for modulating tissue encapsulation of said indwelling catheter.

Claim 28 cancelled.

Claim 29. (4X amended) A method of modulating degradation of an indwelling catheter comprising implanting the indwelling catheter into a patient, wherein the indwelling catheter comprises:

an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; and

an external fitting coupled to the proximal end;

wherein the tissue-contacting surface of the elongate body comprises a polymer intimately mixed with an effective amount of steroidal anti-inflammatory agent such that a non-porous polymer release system is formed with said agent [means] for modulating degradation of said indwelling catheter .

Claim 30-32 cancelled.

Claim 33. (4X amended) A method of making an indwelling catheter comprising:

providing an elongate body having a proximal end, a distal end, a tissue-contacting surface, and at least one interior lumen therethrough; wherein the tissue-contacting surface comprises an overcoat of a polymer intimately mixed with an effective amount of steroidal anti-inflammatory agent such that a non-porous polymer release system is formed with said agent [means] for modulating degradation or tissue encapsulation of said indwelling catheter; and

coupling an external fitting to the proximal end of the elongate body.

Claim 34. The method of claim 33 wherein the step of providing an elongate body comprises intimately mixing the steroidal anti-inflammatory agent with the polymer in a solvent and applying the mixture to the elongate body to form a tissue-contacting surface.

Claim 35 cancelled.

Claim 36. The catheter of claim 13, wherein the polymer is a non-porous polymer.

Claim 37. The catheter of claim 13, wherein the steroidal anti-inflammatory agent is between .1% and 1% of the total solid combined weight of the polymer and the steroidal anti-inflammatory agent.

Claim 38. The catheter of claim 37, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone and beclomethasone.

Claim 39. The catheter of claim 13, wherein the steroidal anti-inflammatory agent is impregnated into the polymer of the tissue-contacting surface.

Claim 40 cancelled.

Claim 41. The method of claim 29, wherein the steroidal anti-inflammatory

agent is impregnated into the polymer of the tissue-contacting surface.

Claim 42 cancelled.

Claim 43. The method of claim 29, wherein the steroidal anti-inflammatory agent is between .1% and 1% of the total solid combined weight of the polymer and the steroidal anti-inflammatory agent.

Claim 44. The method of claim 43, wherein the steroidal anti-inflammatory agent is selected from the group consisting of dexamethasone and beclomethasone.